GUT MUCOSAL ISCHEMIA DURING NORMOTHERMIC CARDIOPULMONARY BYPASS RESULTS FROM BLOOD FLOW REDISTRIBUTION AND INCREASED OXYGEN DEMAND

Impaired gut mucosal perfusion has been reported during cardiopulmonary bypass. To better define the adequacy of gut blood flow and oxygenation during cardiopulmonary bypass, we measured overall gut blood flow and ileal mucosal flow and their relationship to mucosal pH, mesenteric oxygen delivery and oxygen consumption in immature pigs (n = 8). Normothermic, noncross-clamped, right atrium–to–aorta cardiopulmonary bypass was maintained at 100 ml/kg per minute for 120 minutes. Animals were instrumented with an ultrasonic Doppler flow probe on the superior mesenteric artery, a mucosal laser Doppler flow probe in the ileum, and pH tonometers in the stomach, ileum, and rectum. Radioactive microspheres were injected before and at 5, 60, and 120 minutes of cardiopulmonary bypass for tissue blood flow measurements. Overall gut blood flow significantly increased during cardiopulmonary bypass as evidenced by increases in superior mesenteric arterial flow to 134.1% ± 8.0%, 137.1% ± 7.5%, 130.3% ± 11.2%, and 130.2% ± 12.7% of baseline values at 30, 60, 90, and 120 minutes of bypass, respectively. Conversely, ileal mucosal blood flow significantly decreased to 53.6% ± 6.4%, 49.5% ± 6.8%, 58.9% ± 11.6%, and 47.8% ± 10.0% of baseline values, respectively. Blood flow measured with microspheres was significantly increased to proximal portions of the gut, duodenum and jejunum, during cardiopulmonary bypass, whereas blood flow to distal portions, ileum and colon, was unchanged. Gut mucosal pH decreased progressively during cardiopulmonary bypass and paralleled the decrease in ileal mucosal blood flow. Mesenteric oxygen delivery decreased significantly from 67.0 ± 10.0 ml/min per square meter at baseline to 42.4 ± 4.6, 44.9 ± 3.5, 46.0 ± 3.6, and 42.9 ± 3.9 ml/min per square meter at 30, 60, 90, and 120 minutes of bypass. Despite the decrease in mesenteric oxygen delivery, mesenteric oxygen consumption increased progressively from 10.8 ± 1.4 ml/min per square meter at baseline to 13.4 ± 1.2, 15.9 ± 1.2, 16.7 ± 1.4, and 16.6 ± 1.54 ml/min per square meter, respectively. We conclude that gut mucosal ischemia during normothermic cardiopulmonary bypass results from a combination of redistribution of blood flow away from mucosa and an increased oxygen demand. (J THORAC CARDIOVASC SURG 1995;110:819-28)

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Despite advances in cardiopulmonary bypass (CPB) management, patients undergoing CPB are at risk for the development of postperfusion systemic inflammatory response syndrome and multiorgan dysfunction syndrome. In their most pronounced forms, systemic inflammatory response syndrome and multiorgan dysfunction syndrome may be manifested as pulmonary, renal, and gastrointestinal tract dysfunction and hemodynamic instability in the postoperative period.[1] The initiation of these responses is often attributed to whole-body inflammatory reactions caused by extensive blood-surface interactions,[2] activation of the complement system and polymorphonuclear leukocytes,[3, 4] oxy-

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Supported in part by a grant from the American Heart Association (92G-621).

Presented at the Surgical Infection Society Fourteenth Annual Meeting, April 27-31, 1994, Toronto, Ontario, Canada.

Received for publication Sept. 2, 1994.

Accepted for publication Dec. 22, 1994.

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0022-5223/95 $5.00 + 0 **12/1/63290**

gen free-radical generation,[5] and release of cytokines.[6, 7]

Recently, the development of systemic inflammatory response syndrome and multiorgan dysfunction syndrome in critically ill patients has been attributed to pathophysiologic changes in the gut.[8] Gut ischemia can jeopardize the integrity of the mucosal barrier and increase the prevalence of bacterial translocation and endotoxin absorption from the gut.[9, 10] Meanwhile, impaired mucosal perfusion has been reported during experimental and clinical CPB with the use of laser Doppler flowmetry.[11-14] Fiddian-Green and Baker,[15] with use of gastrointestinal tract tonometers to show a decrease in gastric mucosal pH, an indicator of gut mucosal ischemia, positively correlated gastric mucosal hypoperfusion with increased infections and gastrointestinal tract complications after cardiac operations. In contrast, early work on regional perfusion during extracorporeal circulation with the venous outflow[16] and microsphere[17] techniques showed an increase in blood flow to the gut in canine and primate models, yet gut oxygen consumption (Vo_2) was decreased in the canine model, suggesting shunting of blood flow away from the metabolically active gut mucosa.

Changes in gut organ blood flow and Vo_2 during CPB have not been quantitatively defined. Hypothermic CPB has been shown to cause an initial decrease in gut Vo_2 followed by a subsequent increase with rewarming.[13] The relationship between total gut or mucosal blood flow and gut metabolism is important in understanding the mechanism of postperfusion systemic inflammatory response syndrome and multiorgan dysfunction syndrome and in seeking efforts to reduce the associated morbidity and mortality. In the present study, we investigated the effects of normothermic CPB on total mesenteric blood flow, fractional blood flow to different regions of the gut, gut mucosal pH, and mucosal blood flow and their relationship to gut Vo_2.

Material and methods

The experimental protocol was approved by the Animal Care and Use Committee of the University of Texas Medical Branch, Galveston, Tex. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985).

Studies were done in eight female immature Yorkshire pigs weighing 25.6 ± 4.3 kg. After an overnight fast, pigs were sedated with intramuscular ketamine (7.5 mg/kg) and the lungs mechanically ventilated with 2.0% to 2.5% isoflurane after endotracheal intubation. The pigs were then instrumented with femoral arterial and venous catheters and a pulmonary arterial catheter with an on-line O_2 saturation probe tip (Opticath, Abbott, Mountain View, Calif.). A left flank incision allowed retroperitoneal exposure of the superior mesenteric artery (SMA) and a transit-time ultrasonic flow probe (Transonic, Ithaca, N.Y.) was placed on the vessel at its origin from the abdominal aorta. Through the same incision, intraperitoneally, a purse-string suture was made on a tributary mesenteric vein through which an infant feeding catheter was placed at a length of 15 to 20 cm to reach the portal vein for retrieval of blood samples. A laser Doppler flow probe (LDF 1000, Transonic) was placed directly on the ileal mucosa via an antimesenteric enterotomy with the laser sensor secured facing the mucosa. An intestinal tonometer (Tonometrics, Bethesda, Md.) was placed into the lumen of the distal ileum through the same enterotomy. Tonometers were also guided into the stomach (per os) and rectum (per rectum). A 30-minute stabilization period was allowed before baseline systemic and splanchnic hemodynamic values and arterial, mixed venous, and portal venous blood gas measurements were recorded.

Beef lung heparin (400 IU/kg, Upjohn, Kalamazoo, Mich.) was given for systemic heparinization, followed by subsequent administrations to maintain the activated clotting time (model 400, Hemochron, Edison, N.J.) greater than 450 seconds. Normothermic, nonpulsatile, noncross-clamped CPB was initiated with two-stage single venous cannulation (34F, Bard, Tewksbury, Mass.) and aortic arch perfusion (21F, Argyle, St. Louis, Mo.). A membrane oxygenator with an integral heat exchanger (Plexus, Irvine, Calif.), a roller pump (model 5000, 3M/Sarns, Ann Arbor, Mich.), and an in-line arterial filter (Pall, Fajardo, Puerto Rico) were used in the perfusion circuit (Tygon, Akron, Ohio). The CPB circuit was primed with 1000 ml Plasmalyte solution (Baxter, Deerfield, Ill.) and 500 ml 6% hetastarch (Du Pont, Wilmington, Del.). CPB flow was maintained at 100 ml/kg per minute to keep the mixed venous oxygen saturation (Svo_2) greater than 70% per the protocol. Standard perfusion parameters of Svo_2, mean arterial pressure, central venous pressure, and hematocrit were measured at 30, 60, 90, and 120 minutes of CPB. Blood flow and gastrointestinal tract mucosal pH measurements were also recorded at baseline and every 30 minutes during CPB. No vasoactive drugs or blood were used. At the end of the 120-minute bypass period, animals were killed with 10 ml intravenous saturated KCl.

Mean arterial and central venous pressures were measured with the use of transducers (P23, Statham Gould, Oxnard, Calif.) connected to a multichannel pen recorder (model 7758, Hewlett-Packard, Waltham, Mass.). Cardiac output was determined by the thermodilution technique with a cardiac output computer (Oximetrix 3, Abbott, North Chicago, Ill.). Arterial, mixed venous, and mesenteric venous blood gas values were measured with a blood gas analyzer and Co-Oximeter (system 1302 and model 282, Instrumentation Laboratory, Lexington, Mass.) and corrected to the animal's temperature.

Gut oxygen delivery (Do_2) and Vo_2 were determined by the following equations:

$$\text{Gut } Do_2 \text{ (ml/min/m}^2\text{)} = \frac{[(Sao_2 \times 0.134 \times Hgb) + (Pao_2 \times 0.003)] \times Qm}{SA}$$

and

$$\text{Gut } Vo_2 \text{ (ml/min/m}^2\text{)} = \frac{[(Sao_2 - Spo_2) \times 0.134 \times Hgb + (Pao_2 - Ppo_2) \times 0.003] \times Qm}{SA}$$

where Sao_2 and Spo_2 are the arterial and portal blood O_2 saturation (percentage), Pao_2 and Ppo_2 are the arterial and portal blood O_2 partial pressures (millimeters of mercury), Hgb is the hemoglobin concentration (grams per deciliter), Qm is the SMA blood flow (liters per minute), and SA is the body surface area (square meters).

Mucosal pH was calculated on the basis of the measurement of the CO_2 tension (Pco_2) from samples of saline solution in the silicone balloon catheters positioned in the lumen of the stomach, ileum, and rectum. The silicone balloon, which is permeable to CO_2, is filled with saline solution. Because CO_2 is a readily diffusible gas, Pco_2 of the saline solution in the silicone balloon equilibrates with the intraluminal Pco_2 of that intestinal segment, which, in turn, is in equilibrium with the Pco_2 of the mucosa.[15] Samples of the saline solution were allowed to equilibrate with the mucosa for 30 minutes, and tonometrically measured Pco_2 and the concomitantly measured arterial $[HCO_3^-]$ concentration were then substituted into the Henderson-Hasselbalch equation to obtain the mucosal pH value at baseline and every 30 minutes during CPB as follows:

$$pH = 6.1 + \log\left(\frac{[HCO_3^-]}{Pco_2 \times 0.03}\right)$$

where $[HCO_3^-]$ is the arterial bicarbonate concentration (milliequivalents per liter); Pco_2 is that value measured in the aliquot obtained from the tonometer equilibrating balloon.

Blood flow to specific regions of the splanchnic viscera was measured by the radioactive microsphere technique.[18] Four different isotopes were used in each animal to determine fractionated blood flow at different time points. Microspheres (15 ± 3 μm diameter) labeled with ^{141}Ce, ^{85}Sr, ^{95}Nb, and ^{46}Sc were suspended in 10% dextran with polysorbate 80 (Tween 80, DuPont, Boston, Mass.). They were injected into the left atrium (at baseline) and arterial cannula at 5, 60, and 120 minutes of CPB. Calibration of blood flow was done by withdrawing a reference sample of aortic blood at 7.5 ml/min starting just before injection of the microspheres and continuing for 3 minutes. Approximately 4 to 8 × 10^6 microspheres were injected with each measurement. This ensured that at least 400 microspheres per gram were lodged in most tissue samples or in the arterial reference for a 95% confidence of an error less than 10%. Blood flow to right and left kidneys was compared to confirm adequate aortic mixing of microspheres during injection.

Table I. *The main physiologic variables during CPB*

Minutes of bypass	*MAP (mm Hg)*	*Svo_2 (%)*	*Hct (%)*
Baseline	77.0 ± 5.5	86.0 ± 2.5	28.4 ± 1.5
30	54.6 ± 7.9*	75.0 ± 2.4†	15.6 ± 1.3†
60	62.3 ± 8.7*	73.8 ± 2.0†	16.8 ± 0.8†
90	51.9 ± 5.2*	71.5 ± 2.1†	17.5 ± 0.9†
120	52.5 ± 6.8*	71.4 ± 2.3†	15.9 ± 0.7†

MAP, Mean arterial pressure; *Hct*, hematocrit.
*$p < 0.05$ versus baseline value.
†$p < 0.01$ versus baseline value.

At autopsy, multiple full-thickness wall tissue samples (2 × 2 cm) were taken from stomach, duodenum, jejunum, ileum, and colon. All the tissue samples were placed into preweighed polypropylene tubes together with the reference blood samples. Individual isotope activities were determined by a gamma counter (model A5550, Packard, Laguna Hills, Calif.). Blood flow was calculated by the following formula and is reported as milliliters per minute per 100 grams of tissue:

$$QT = \frac{Mt \times Qref \times 100}{Mref \times Wt}$$

where Qt is tissue blood flow (milliliters per minute per 100 grams tissue), Mt is microsphere radioactivity in the tissue sample (counts per minute), Qref is the withdrawal rate of the aortic reference sample (milliliters per minute), Mref is the microsphere radioactivity in reference blood samples (counts per minute), and Wt is the sample weight (grams).

Data are expressed as mean plus or minus the standard error of the mean and were displayed and analyzed by SigmaPlot and SigmaStat programs (Jandel Scientific, San Rafael, Calif.). Comparisons with baseline values were made by one-way analysis of variance with Dunnett's test, with time treated as a repeated measurement factor. Significance was accepted with $p < 0.05$.

Results

The main physiologic variables during CPB are summarized in Table I. During CPB at a flow rate of 100 ml/kg per minute, mean arterial pressure was maintained higher than 50 mm Hg and Svo_2 higher than 70%, as dictated by the experimental protocol. The expected hemodilution occurred and the hematocrit value was maintained higher than 15%.

Changes in overall and mucosal gut perfusion, represented by SMA blood flow and ileal mucosal blood flow, respectively, are shown in Fig. 1. SMA blood flow was 0.48 ± 0.03 L/min at baseline but significantly increased to greater than 130% of baseline values during CPB. The nature of laser Doppler flowmetry does not lend itself to calibration in milliliters per minute and results are only pre-

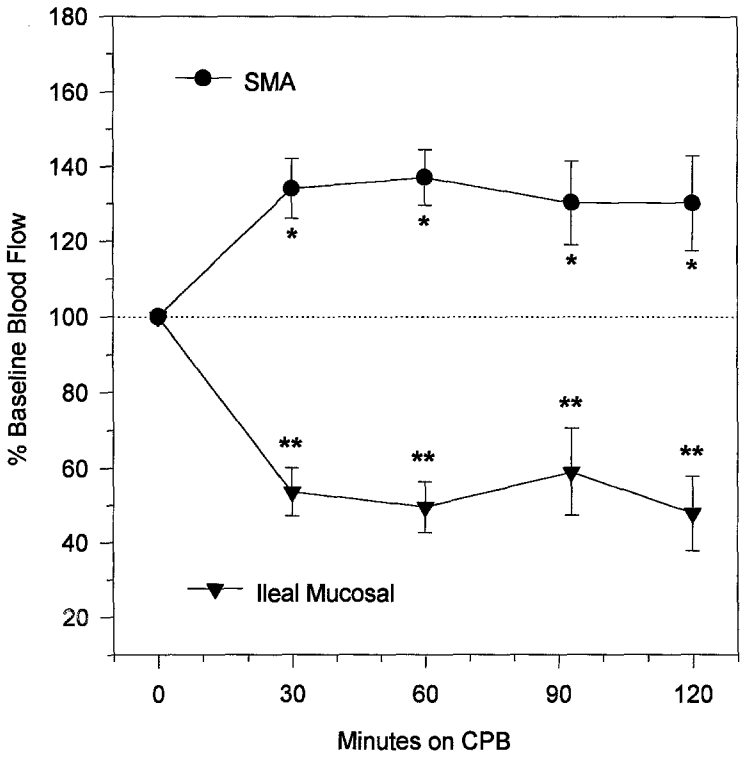

Fig. 1. SMA and ileal mucosal blood flow during CPB. SMA blood flow significantly increased to greater than 130% of baseline values, whereas ileal mucosal blood flow significantly decreased to approximately 50% of baseline value. $*p < 0.05$ versus baseline value; $**p < 0.01$ versus baseline value.

sented as percent of the baseline value. Despite the increase in SMA blood flow, ileal mucosal blood flow significantly decreased to approximately 50% of the baseline value during CPB. The decrease in ileal mucosal flow during bypass is consistent with the significantly decreased Svo_2 in the portal venous blood during CPB (Fig. 2).

Changes in the gastrointestinal tract mucosal pH during CPB as measured by tonometry are shown in Fig. 3. Gastric, ileal, and rectal pH values all decreased significantly from baseline values during CPB.

The pH values of arterial, mixed venous, and portal venous blood at baseline and during CPB are shown in Fig. 4. Arterial and mixed venous blood pH values remained normal during CPB. However, portal venous blood pH values decreased significantly from 7.37 at baseline to approximately 7.30 at 90 and 120 minutes of CPB.

Changes in blood flow from baseline to the splanchnic organs as measured by microspheres are presented in Table II. Baseline blood flow to the duodenum, jejunum, ileum, and colon was 40.4 ± 5.9, 47.9 ± 13.3, 42.7 ± 7.9, and 35.4 ± 7.2 ml/min per 100 grams of tissue, respectively. Blood flow significantly increased in the proximal portions of the gut, the duodenum and jejunum, during CPB, whereas it remained unchanged in the distal portions, the ileum and colon.

Fig. 5 shows the relationship of gut Do_2 and Vo_2 during CPB. There was a significant decrease in gut Do_2 during CPB; however, gut Vo_2 increased progressively and independently of the decrease in gut Do_2. The gut Do_2/Vo_2 ratio also decreased progressively during CPB, but remained greater than 2.9 ± 0.3 throughout CPB.

Discussion

An increase in mucosal permeability has been implicated for translocation of bacteria and endotoxins and subsequently for contributing to the systemic inflammatory response syndrome and multiorgan dysfunction syndrome in patients undergoing CPB.[8] The intestinal mucosal barrier consists of mucoid secretions and proliferative epithelial cells with tight intercellular junctions. The barrier is

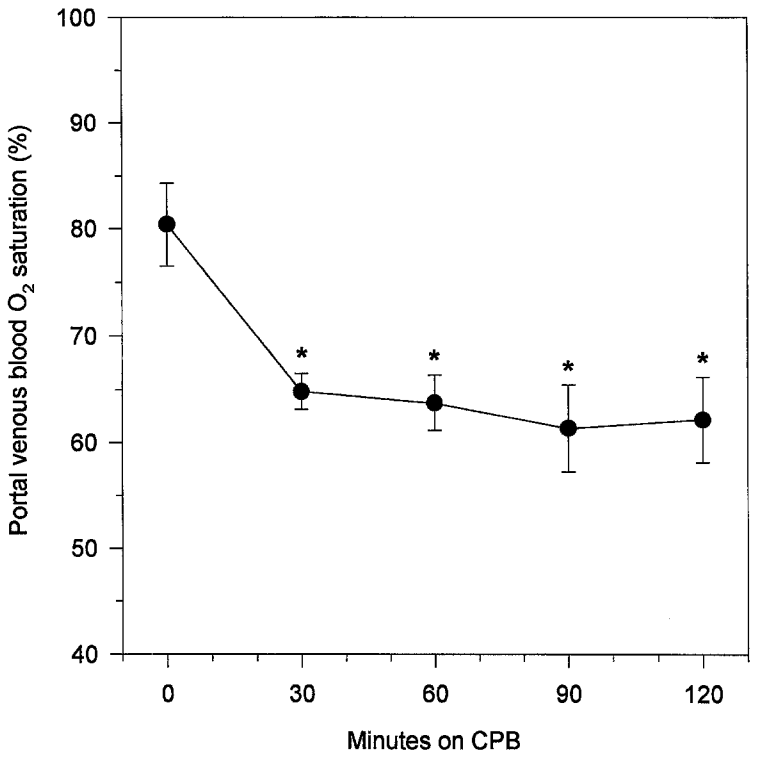

Fig. 2. Changes in portal blood O_2 saturation during CPB. Consistent with decrease in mucosal blood flow, portal blood O_2 saturation significantly decreased during CPB. $^*p < 0.05$ versus baseline value.

characterized by its relative impermeability to most solutes and active transport mechanisms of selected ones.[19] This barrier, along with other functions, prevents bacteria and their endotoxins from entering the portal and systemic circulation.

Our earlier[11, 12] and present studies have shown that normothermic CPB is associated with gut mucosal ischemia despite "adequate" global perfusion: there is normal or even increased overall blood flow through the SMA, but the gut mucosa remains ischemic, as evidenced by mucosal blood hypoperfusion measured by laser flowmetry and mucosal acidosis measured by tonometry. Coinciding with this observation are results of clinical studies that show similar evidence of gut mucosal ischemia during CPB. Fiddian-Green and Baker,[15] using the orogastric tonometer, reported a 50% prevalence of mucosal acidosis as manifested by a decrease in gastric mucosal pH values from 7.52 before CPB to less than 7.32 by the end of CPB in 85 patients. Andersen and associates[20] found that the gastric mucosal pH in 10 patients decreased from 7.45 before CPB to 7.30 at 1 hour after CPB. In a series of eight patients, Niinikoski and Kuttila[21] showed that the gastric pH decreased progressively during cardiac operation and remained low after operation. In 10 patients undergoing coronary artery bypass grafting Ohri and associates[14] measured a 51% decrease in gastric mucosal blood flow with the use of laser Doppler flowmetry, a finding similar to our experimental data. Although gut mucosal ischemia during CPB is demonstrated in immature swine in our studies, the trend to or severity of mucosal ischemia and acidosis in adult patients undergoing cardiac operations in the studies cited is similar.

Our present study demonstrates that mucosal ischemia during normothermic CPB results from the combination of mucosal hypoperfusion and increased gut Vo_2. With the measured increase in overall gut blood flow, mucosal hypoperfusion is likely to be the result of mucosal vasoconstriction and blood redistribution away from the mucosa. A host of vasoactive substances (hormones, autacoids, and cytokines) are known to be released or altered during CPB that can potentially affect regional blood flow at the macrocirculatory and microcirculatory levels,[22] and these substances can also be candidates for vasoconstriction of gut mucosa. Main vasoconstrictors that have been shown to be released during CPB include vasopressin,[23] cat-

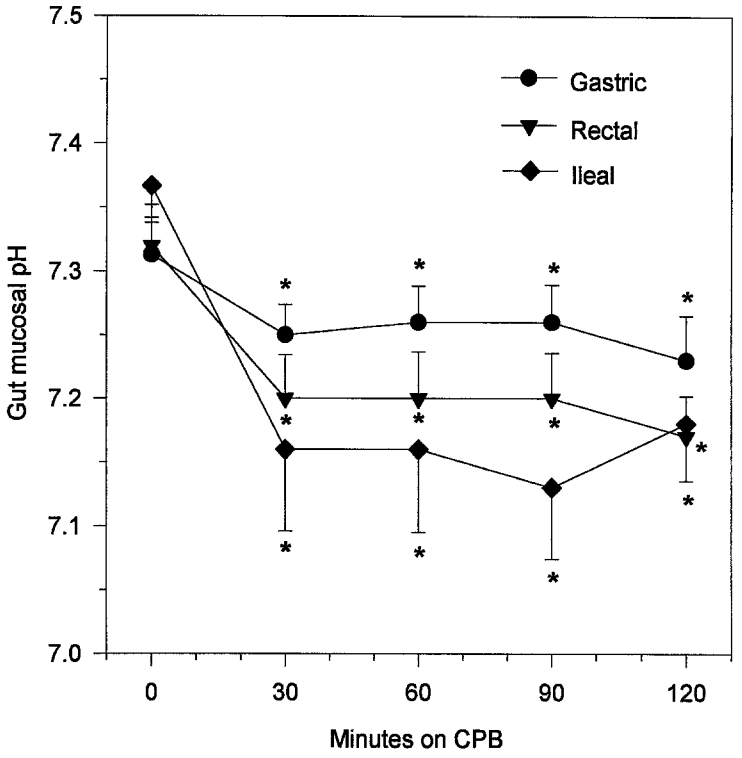

Fig. 3. Gut mucosal pH values during CPB. Gastric, rectal, and ileal mucosal pH values all decreased significantly during CPB. $*p < 0.05$ versus baseline value.

echolamines,[24] and thromboxane A_2 and B_2.[25, 26] In a model of experimental CPB identical to that of the current study, our group found elevated levels of a highly vasoconstrictive thromboxane compound in association with the decrease in mucosal blood flow.[11] CPB in human beings is associated with an increase in circulating tumor necrosis factor formation that can activate other vasoactive substances.[7] Initiation of CPB is also associated with activation of complement (C3a and C5a),[27] which causes vasoconstriction and increased capillary permeability.[28] Loss of pulsatility in the renal arteries and low perfusion can trigger the renin-angiotensin-aldosterone system and lead to increased production of angiotensin II,[29, 30] which is also a potent splanchnic vasoconstrictor. Antagonists of such vasoconstrictive mediators and the effect of pulsatile blood flow during CPB on mucosal perfusion, therefore, warrant further studies.

Increased gut Vo_2 was another contributing factor to mucosal ischemia in our study. During normothermic CPB, gut Vo_2 progressively increased despite the decrease in gut Do_2. Increased total body Vo_2 and a higher metabolic rate have been shown in patients after cardiac operations.[31-34] Such changes in Vo_2 may be a result of inflammatory responses initiated during CPB. Hypothermia, however, may diminish this response. Indeed, during experimental hypothermic CPB,[13] gut Vo_2 initially decreased when the animal was cooled, but surged to 33% higher than the baseline value during rewarming.

Studies on the Do_2-Vo_2 relationship have shown that Vo_2 is independent of Do_2 as long as the Do_2/Vo_2 ratio is higher than a critical value, below which anaerobic metabolism occurs and Vo_2 decreases concomitantly with Do_2.[35, 36] Measurements of Do_2 and Vo_2 with instrumentation similar to that used in the present study suggested that the critical value of the Do_2/Vo_2 ratio is approximately 1.3 for the whole body and 1.5 for the gut, and these ratios increased to 1.9 and 2.2, respectively, during experimental sepsis.[37] Sepsis also increases total body and gut Vo_2 itself.[37, 38] During CPB, the abrupt decrease in O_2 delivery because of hemodilution coupled with increased oxygen demand could result in pathologic oxygen supply dependency that will limit the increase in Vo_2.[39] In our model of normothermic bypass, the gut Do_2/Vo_2 ratio remained greater than 2.9 and Vo_2 increased progressively throughout the course of CPB, suggesting high gut metabolism,

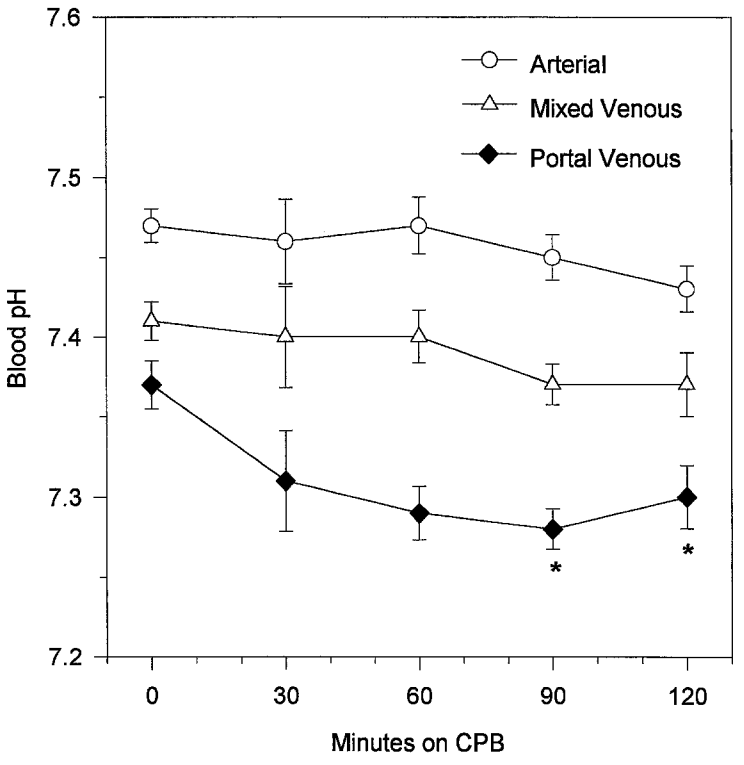

Fig. 4. Arterial, mixed venous, and portal venous blood pH values during CPB. Although arterial and mixed venous blood pH values remained relatively normal throughout CPB, portal venous blood pH value decreased significantly at 90 and 120 minutes of bypass. *$p < 0.05$ versus baseline value.

probably as a result of an inflammatory response. Such inflammatory responses and their effect on the gut Do_2-Vo_2 relationship during CPB remain to be further defined. In addition, hypothermic CPB, with its effect on reducing the oxygen demand of the gut tissue, may partially protect the gut from mucosal ischemia.

The gut lumen is a rich source of gram-negative bacteria that constantly release lipopolysaccharide from their outer membrane; these endotoxins normally cannot cross the mucosal barrier because of their relatively large molecular size. Even if some small amounts cross, they are efficiently scavenged by the reticuloendothelial system. Mucosal ischemia occurring during CPB may greatly increase mucosal permeability.[14, 40] Increased mucosal permeability, along with a known dysfunction of the hepatic reticuloendothelial system[41] and the systemic immunosuppression[42] associated with CPB, may allow bacteria and particularly smaller endotoxins to enter the portal and systemic circulation. In turn, bacteremia or endotoxemia, or both, exacerbate mucosal ischemia and promote translocation[43, 44] and further increase the metabolic demand for oxygen in

Table II. *Blood flow to the gut measured by microspheres (percent of baseline)*

Minutes of CPB	*Duodenum*	*Jejunum*	*Ileum*	*Colon*
5	150 ± 13*	131 ± 10*	113 ± 14	107 ± 14
60	148 ± 14*	108 ± 16	89 ± 12	101 ± 11
120	127 ± 12*	129 ± 15*	102 ± 10	106 ± 10

*$p < 0.05$ versus baseline value.

splanchnic organs.[45] This hypothesis is supported by the fact that endotoxin levels during CPB are preferentially higher in the blood of the splanchnic circulation,[20] and the degree of mucosal acidosis during CPB correlates well with the risk for subsequent complications or death.[46]

In summary, the present study demonstrates significant gut mucosal ischemia during normothermic CPB despite normal indices of global perfusion. Factors that contribute to mucosal ischemia include redistribution of blood flow away from the mucosa, possibly because of regional vasoconstriction, and increased total gut metabolism. Gut mucosal ischemia during CPB may lead to mucosal barrier malfunction and translocation of bacteria or endo-

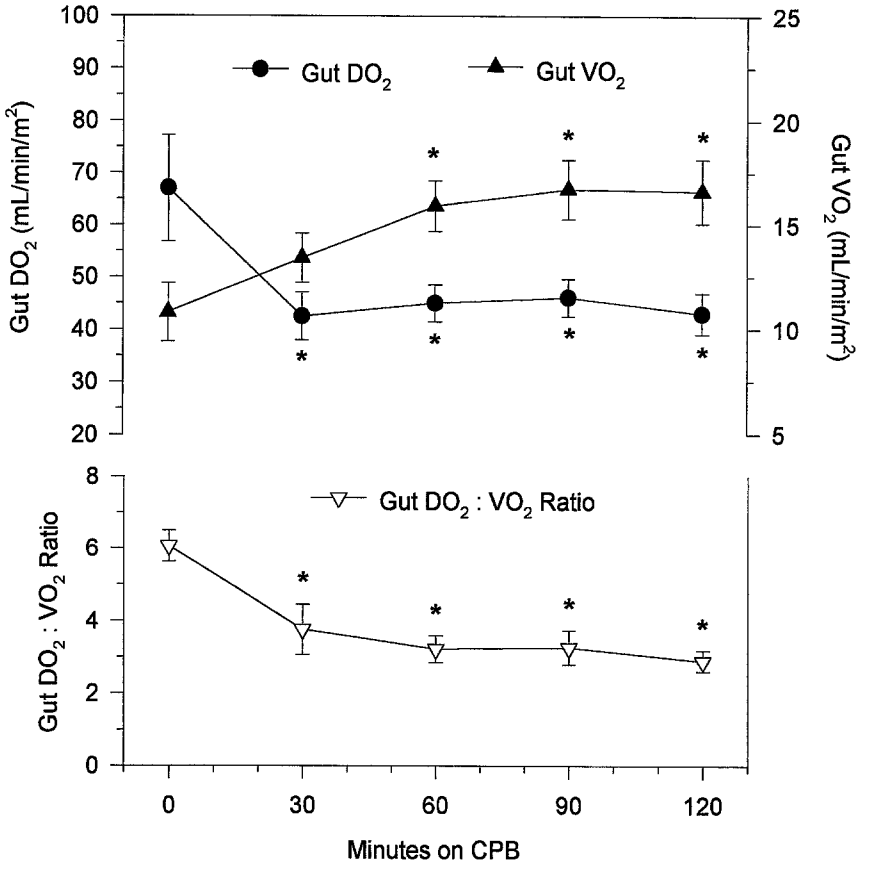

Fig. 5. Changes in gut Do_2 and Vo_2 during CPB. Gut Do_2 significantly decreased during CPB, but gut Vo_2 increased progressively and independently of the decrease in gut Do_2. Gut Do_2/Vo_2 ratio decreased progressively during CPB, but remained greater than 2.9. $^*p < 0.05$ versus baseline value.

toxins, or both, causing postperfusion systemic inflammatory response syndrome and multiorgan dysfunction syndrome. Strategies to effectively reduce redistribution of intestinal blood flow during CPB may decrease the resultant morbidity and mortality in patients at high risk.

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